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PENICILLIN--A WARTIME ACCOMPLISHMENT[1]

By Robert D. Coghill[2], Northern Regional Research Laboratory,
and Roy S. Koch, Aromatics and Drugs Branch, Chemicals Division,
Civilian Production Administration, formerly WPB

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In April 1944, when the first extensive report on penicillin production was made (1), the industry was in the throes of a rapid expansion to meet wartime needs. Today, with the two wars rapidly receding into the background, it stands solidly on its own feet as one of the great achievements of the period, and one which will continue to have a mitigating effect on human suffering. We have asked our authors to bring the story up to date, and they have complied with this article. In their own words, "It is a very satisfying tale to relate."

Penicillin production has increased from 18.7 billion units in February 1944 to 405 billion units in February 1945 and 647 billion units in June of the same year. Table 1 indicates this tremendous upsurge in production, the figures for the last 3 months being estimates.

One billion units will treat an average of 1,000 serious cases, or an average of 1 million units per case.

It is estimated that in 1945 the production of penicillin will be more than 6,800 billion units, or over four times the 1944 production of 1,633 billion units. The decrease in production during the July to October period is temporary and attributed to corn steep liquor difficulties arising from the quality of corn available for processing. Better quality corn will be available in December when penicillin production should reach 700 billion units. The capacity of present facilities under current operating conditions is estimated at 800 billion units per month, but further processing improvements could easily increase this figure to 1,000 or 1,200 billion units per month. The penicillin produced in 1944 was worth approximately $35,000,000, while the value of the greatly increased production in 1945 is estimated at only $60,000,000 because of concurrent price reductions. The impact of sales of new penicillin dosage forms may well make penicillin retail sales exceed those of any other medicinal product.

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[2] Now Associate Director of Research, Abbott Laboratories, North Chicago, Illinois.

Table 1.- Monthly U. S. Production of Penicillin

Unit: billion units

1943	
January to May, inclusive	0.400
June	0.425
July	0.762
August	0.906
September	1.787
October	2.872
November	4.846
December	9.194
Total	21.192
1944	
January	12.550
February	18.726
March	32.191
April	74.963
May	94.132
June	117.527
July	128.972
August	163.480
September	196.574
October	229.950
November	270.584
December	293.736
Total	1,633.385
1945	
January	394.113
February	405.156
March	460.958
April	510.960
May	615.071
June	646.817
July	616.897
August	636.51
September	586.37
October (est.)	620.00
November (est.)	660.00
December (est.)	700.00
Total (est.)	6,852.000

The penicillin program represents an investment of approximately $25,000,000 in buildings and equipment. Individual commercial plants have ranged in cost from $350,000 for small surface culture facilities to over $3,000,000 for large installations employing the deep-tank culture method. That the Government financed less than one third of this total investment indicates the firm and continuous basis anticipated by industrial management for penicillin production.

Price and Quality

The first penicillin was priced at $20 per 100,000 units, but as a result of technological improvements in culturing and extraction, the cost spiraled downward until today it is available for as little as $0.60 per 100,000 units, with the Government procuring it for less. Costs are expected to be reduced still further. Production increased 1,610 times in 24 months from 0.4 billion units in June 1943 to 647 billion units in June 1945, with concomitant improvement in quality. Originally, penicillin of 100 units per mg. was acceptable for clinical use, but by late 1944, 300 units per mg. was the required standard. Today the average potency of penicillin ranges from 500 to 800 units per mg., with 1,000 unit per mg. material being commonly produced by some manufacturers. The expiration date, showing the effective life of penicillin, gradually has increased from the original 3 months until, at present, manufacturers are permitted by the Food and Drug Administration to use an 18-month dating. Thus, while production rose phenomenally and the price declined over 95 percent, the potency in terms of units per mg. improved five- to tenfold.

Production Methods

Two years ago there were two main methods of producing penicillin, with two minor methods in the background. Concerning the latter two methods (both modifications of the surface culture technique), the percolation process has never proved to be practicable, and the bran process has recently been abandoned after exhaustive trials. The so-called bottle method (surface growth in glass bottles) has gradually given away to deep culture in vat fermentors, which range in capacity from 1,000 to 12,000 gallons. This trend to the submerged process has been so marked that there is only one bottle plant operating in the United States today. The reason for this shift in emphasis is that early difficulties in the operation of the vat fermenters have been overcome, thus nullifying the original chief argument in favor of the bottle process--namely, that we knew that penicillin could be produced by this method. A further unexpected dividend to the "submerged" producers has been the discovery of new organisms which give much better yields than the best surface cultures. There is no question but that, before many months, penicillin production in the United States will be by the submerged process only.

Aside from the success of the submerged process, probably the outstanding contribution to the penicillin industry over the past two years has been the development of better mold strains. This has come about through continued research at the Northern Regional Research Laboratory, as well as through a series of projects set up and supported by the Office of Production Research and Development of WPB. K. B. Raper, of the Northern Regional Research Laboratory, isolated several hundred new strains of penicillin-producing organisms from soils obtained from all over the world (through the courtesy of the Army Transport Command). This work demonstrated that good cultures were of extremely wide distribution. The travesty of the situation, however, was that the best culture of all was found on a moldy canteloupe picked up in a Peoria fruit market. From this culture, by a long and tedious process of selection, was obtained a strain, Penicillium chrysogenum, NRRL 1951.B25, which gave much higher yields of penicillin in submerged culture than had any previous organism.

The OPRD projects, referred to above, were carried on at Stanford University, the University of Wisconsin, the University of Minnesota, and the Carnegie Institution at Cold Spring Harbor, New York. The objective was to obtain better penicillin-producing strains of mold, either by isolation from nature or by the production of mutations from previously known organisms by means of light, X-ray, or chemicals. Among tens of thousands of mutants examined, a number of high producing strains were thus obtained, the best of these being an X-ray induced mutant of P. chrysogenum, NRRL 1951.B25, which was produced by Dr. Demerec of the Carnegie Institution. This organism, known as X-1612, is now very widely used by the penicillin industry and is producing what formerly would have been considered fantastic yields--as much as 500 units per ml. in pilot-plant equipment and consistent yields of over 300 units per ml. in the large-sized fermenters of some industrial plants.

No material changes in the gross makeup of the culture medium have been made in the past two years. The majority of the producers still use the steep liquor-lactose medium originally devised by Moyer (3). Small differences in the concentrations of nutrients are noted here and there, but these are of minor consequence. The practice of adding certain organic chemicals in very small concentration has proved effective in increasing total penicillin yields and modifying the type of penicillin produced. Although the identity of these chemicals is still a confidential matter, it is presumed that this information can be made public before too long.

As penicillin production climbed, more and more raw materials in critical supply, such as acetone, amyl acetate, lactose, and activated carbon, were required. Lactose production was practically doubled in a year by the War Food Administration, and lactose was placed under allocation for a time to insure penicillin requirements. Acetone and amyl acetate were similarly allocated by WPB while facilities were installed by a number of producers to reduce consumption and to improve recovery of these critical solvents. Activated carbon production was increased, and a research program at Pennsylvania State College revealed that, in most plants, certain types of activated carbon were interchangeable. By these and other means, raw materials were made available for penicillin, so that production could continue its rise without being impeded by the raw material shortages which sometimes delayed other urgent programs.

The quantity and quality of the agitation and aeration in the fermenter are among the most important factors in obtaining high penicillin yields. These two interrelated functions must be evaluated for each size and shape of fermenter, and it is through the successful solution of this problem that many plants have greatly increased their output.

Recovery

The recovery of the penicillin from the culture liquor has been changed only in detail rather than in principle during the past year and a half. Some producers extract the free penicillin acid directly from the broth with solvents, while others prefer first to remove the penicillin by adsorption on charcoal, followed by elution before extraction. An OPRD project at Pennsylvania State College performed yeoman service in developing much information on recovery procedures which was of value to the producers. Recovery yields now vary from 40 to 70 percent of the penicillin obtained in the broth, an average of above 50 percent probably obtaining. What is not reflected in this figure, however, is the great improvement in quality which was referred to above.

A new and improved drying method, based on electronic heating, has been developed by the RCA Laboratories (2). This process greatly decreases the time as well as the floor space required in this crucial recovery step.

Chemistry

The chemistry of penicillin, as of this writing, is still classified as secret, with the expectation that the information will be released within the near future. One fact, however, which for a variety of reasons has now emerged, is that, as in the case of the B vitamins, there is a multiplicity of penicillins. These compounds, all characterized by minor variations on the same fundamental structure, are produced in varying proportions on different media and by different strains of the mold. The four principal penicillins are known in this country as F, G, X, and K, and in the United Kingdom as I, II, III, and IV, respectively. When existing secrecy regulations have gone the way of other necessary wartime restrictions, these designations can be replaced by accepted chemical nomenclature. These various penicillins have markedly different chemical and biological reactivities, which are important from the point of view of the plant superintendent as well as, probably, that of the physician. For instance, when assayed against Staphylococcus aureus with Penicillin G as the standard, they vary in activity from 850 to 2,300 units per mg. The picture relative to their clinical use is not yet clear because of the fact that most commercial preparations are mixtures containing unknown proportions of the various penicillins. The result is that physicians have not known which penicillin they were using. There is some indication that Penicillin X, the easiest to separate from the others, may be of superior value in the treatment of gonorrhea (5,7). The problem of the production of pure penicillins and their subsequent individual clinical evaluation still remains to be solved, at least in large part. However, as long as they are still sold on the basis of units, their differences in potency are not appreciably reflected in the values the patient receives.

Penicillin Standards and Assay

The cylinder-plate technique is still the official method of penicillin assay. In individual plants, however, other methods are more generally used for process control purposes, the most common of these being the turbidimetric method. A variety of chemical methods (still restricted information) and an enzyme method (4) have also been proposed. Any technique, however, which in principle measures the number of penicillin molecules (any chemical or enzymic method), is accurate with respect to units only when one knows the proportions of the various penicillins present in the sample. This is because of the threefold differences in their activities when expressed as units per mg. Inasmuch as it is very difficult to determine these proportions, and many manufacturers do not have these data on their products, a microbiological assay will have to be the final assurance of activity as long as penicillin is sold on a unit basis.

The assay problem is still further complicated because any microbiological method requires the use of a standard penicillin, and various test organisms vary markedly in their response to the different penicillins (6). For instance, using Penicillin G as a standard, Penicillin X is twice as active against a rough strain of Bacillus subtilis as it is against Staphylococcus aureus, whereas Penicillin K is only one third as active. It is thus obvious that for a microbiological assay to be strictly accurate, the standard penicillin should be of the same composition with respect to the individual penicillins as is the unknown. With the number of concerns which are producing penicillin, this is obviously impossible. One has, in this situation, to be satisfied with something less than perfection.

In order to clarify this situation, and, if possible, to recommend an International Standard and an International Unit, the League of Nations Health Organization sponsored a meeting in London on October 16 to 19, 1944. This meeting was presided over by Sir Henry Dale, and the delegates included representatives from England, Canada, Australia, France, and the United States. These delegates recommended to the League of Nations Health Organization that the International Standard should consist of pure sodium Penicillin G, and that the biological activity corresponding to 0.6 microgram of this International Standard should comprise the International Unit. It further stipulated that the test organism for the bio-assay should be either of two specifically mentioned strains of S. aureus. The chief reasons for selecting Penicillin G, rather than one of its analogs, for the International Standard was that it was the major constituent of most of the commercial products produced at that time and was also the easiest to prepare reproducibly in a pure crystalline state. As defined, the International Unit is, as near as can be told, approximately the size of the original Oxford Unit.

The International Standard has since been prepared by F. H. Stodola at the Northern Regional Research Laboratory. It consists of the first crop of crystals resulting from the recrystallization of the pooled samples of sodium Penicillin G generously contributed by manufacturers in the United States and England. A 10-gram sample has been deposited in the National Institute for Medical Research at Hampstead, London, for the use of the Health Organization of the League of Nations and its successor in any new world organization. There is little question but that, as penicillin purification and separation become more advanced, additional penicillin standards will become necessary. The International Standard and Unit are still not official, inasmuch as the League of Nations Health Organization has not as yet ratified the recommendations of the conference.

Therapeutical Usefulness

The place of penicillin in the clinical field has not changed greatly since the time of the last report (1). Its toxicity is negligible, although it arouses an occasional allergic response. Its field of action has not been materially enlarged, the newer developments being its successful use in many cases of bacterial endocarditis and syphilis. In the former condition, penicillin's usefulness depends on the sensitivity of the causative organisms, all of which will not respond. With respect to syphilis, although many early cases have responded in a most gratifying manner, it still remains to be determined how many recurrences will eventuate.

There have been many isolations of what are usually regarded as penicillin-sensitive species of bacteria which, in the language of the bacteriologist, are "fast" or resistant. It has furthermore been conclusively demonstrated that a sensitive strain, by successive exposures to slightly less than lethal concentrations of penicillin, can be converted into a "fast" strain, and it is feared in some quarters that, if penicillin should be made available for purposes of self-medication, many "fast" strains will be spontaneously developed which in time may curtail the effective results which can now be obtained with penicillin therapy.

Because of its instability at the pH of the gastric juice, penicillin was formerly administered intravenously or intramuscularly. More recent work, however, has demonstrated methods of passing it through the stomach unaltered, and it now appears that much penicillin will be administered orally. The doses, however, will probably have to be approximately three times as large. Other effective dosage forms have also been devised and will be referred to below.

Distribution

In July 1943 WPB issued Order M-338, placing penicillin under allocation, and each month thereafter alloted expected production to various claimant agencies, including the Army, the Navy, the U. S. Public Health Service, and the Office of Scientific Research and Development. During 1943 and most of 1944, the armed forces absorbed from 75 to 85 percent of the total supply. Military requirements have gradually decreased until now they amount to less than 30 percent of the monthly production, and further reductions are expected as production increases and procurement contracts are adjusted.

Chester Keefer, of the Committee on Medical Research of OSRD, was in charge of the program for the clinical evaluation of penicillin. From February 1943, before penicillin was placed under allocation by WPB, until May 1, 1944, Dr. Keefer equitably dispensed the civilian supply of penicillin, in order to save lives and at the same time obtain maximum clinical data from the limited quantities obtainable. The available civilian supply by April 1944 was more than could conveniently be released through Dr. Keefer's office, but was less than was necessary for uncontrolled civilian distribution through normal channels of trade. Therefore, the WPB Penicillin Producers Industry Advisory Committee, which had been established in September 1943 to obtain the advice and opinion of representatives of each penicillin producer on production and distribution problems, was asked by WPB to recommend an interim procedure for the civilian distribution of penicillin. This committee formulated a plan, approved by the Government, for limited distribution through certain civilian hospitals during the transition period. The plan called for the establishment of a centrally located office to distribute, each month, the penicillin available for civilian use after military and other governmental requirements had been fulfilled.

WPB therefore established the Civilian Penicillin Distribution Unit in Chicago, under J. N. McDonnell, to clear all orders for penicillin. An advisory panel was appointed, composed of representatives of OSRD, the U. S. Public Health Service, WPB, and the American Medical Association, for the purpose of selecting the first 1,000 hospitals to distribute the initial allotment of penicillin in May, and to assign a monthly quota to each of these hospitals. The monthly quotas for these "depot hospitals," established for the storage and distribution of penicillin, were based on the location and type of hospital, bed capacity, admission rate, population served, and other factors. The quotas for depot hospitals enabled them to supply other hospitals in their area as well as to provide for their own requirements. WPB advised all hospitals of the plan and supplied them with lists of depot hospitals and copies of Dr. Keefer's report on "The Use, Indications, Contraindications, and Mode of Administration of Penicillin." The first report by Dr. Keefer was issued May 1, 1944, and was revised several times, the last revision being that of April 1, 1945. Over 50,000 copies of this report were distributed by WPB to hospitals and physicians. At intervals, as supplies improved, monthly quotas were increased and additional depot hospitals were added until a total of 2,700 were procuring penicillin from the Civilian Penicillin Distribution Unit.

This temporary procedure was in operation from May 1, 1944, to March 15, 1945, and served efficiently to distribute sodium penicillin for parenteral use by the 8,000 hospitals and related institutions in the United States, Alaska, Puerto Rico, Hawaii, and the Virgin Islands. The amounts distributed are shown in Table 2.

Table 2.- Monthly Distribution of Penicillin Through Depot Hospitals by Civilian Penicillin Distribution Unit, WPB

Unit: billion units

1944		1945	
May	12.212	January	35.232
June	14.290	February	38.100
July	15.451	March (1-15)	17.514
August	19.330		
September	20.048		
October	24.950		
November	26.776		
December	29.387		
Total	162.444	Total	90.846

When it became evident in January 1945 that, as a result of increased production, military and other essential requirements having been met, civilians could be allocated greater supplies of penicillin, a plan was developed with the Penicillin Producers Industry Advisory Committee to transfer distribution from the controlled procedure of the Civilian Penicillin Distribution Unit to regular professional and commercial channels. Therefore, on March 15, WPB released for civilian distribution, through regular trade channels, 128 billion units, representing approximately 3.5 times the amount released by the Civilian Penicillin Distribution Unit in February. WPB subsequently released additional quantities each month until a total of 1,375 billion units had been released for civilian parenteral use from March 15 to August 1, 1945. From surveys of distribution and producers' stocks, made June 1 and August 1, it was evident that domestic civilian parenteral consumption was averaging 200 billion units per month.

Consumption of parenteral forms of penicillin for veterinary purposes is small but is expected to rise as supplies increase, prices decline, and veterinary use is more definitely determined.

Dosage Forms

By June 1945 it became apparent that after military requirements and civilian and export demands were fulfilled, there was a considerable quantity of penicillin available (as a result of increased production) for use in preparing other dosage forms, such as tablets, capsules, lozenges, dental preparations for oral use, and ophthalmic and topical ointments. Such preparations were in demand because of their convenience for physicians and patients. On June 20, 1945, penicillin manufacturers were authorized by WPB to use and sell penicillin for compounding such pharmaceutical preparations, with the provisos that such new preparations have Food and Drug Administration approval and that they not be shipped prior to August 1, 1945. The penicillin producers, through their Industry Advisory Committee, agreed that there might not be sufficient penicillin to supply initial demands for all new products containing penicillin, but guaranteed that adequate supplies of penicillin would be packaged in a form for parenteral use. This promise has been fulfilled, and parenteral penicillin is readily available. It will continue to be so because of the essentiality of the parenteral type of medication regardless of the effect of oral and other dosage forms on the penicillin market.

Food and Drug Administration Regulations

The new penicillin dosage forms did not go on sale August 1, 1945, for on July 6, 1945, President Truman signed a bill (H. R. 3266) amending the Food, Drug and Cosmetic Act of June 25, 1938, and providing for certification of penicillin and penicillin products. Prior to the signing of H. R. 3266, the Food and Drug Administration had tested all lots of each manufacturer's penicillin under a wartime agreement with the Army, the Navy, and WPB. When the quantity of penicillin available to civilians increased, the FDA felt that methods available to it for checking interstate shipments of other drug products would not be effective for the control of penicillin and its products. FDA, therefore, requested Congress to authorize pretesting before marketing. If the potency and purity established by the new regulations for penicillin and the various products are satisfactory, each lot is certified by the FDA. The nominal costs of the assay are borne by the manufacturer. The FDA issued monographs effective September 11, 1945, and certified lots of the following penicillin preparations which were available in September:

- Sodium penicillin
- Calcium penicillin
- Penicillin in oil and wax
- Penicillin ointment (ophthalmic and general purpose)
- Penicillin capsules in oil
- Penicillin tablets (buffered)
- Buffered penicillin
- Penicillin troches
- Penicillin dental cones

The FDA has established a Division of Penicillin Control and Immunology, with Henry Welch as chief, to handle penicillin, other antibiotics, antiseptics, and immunological problems.

Export

In the early days of penicillin production, emergency appeals from friendly and neutral countries were handled by the State Department, and penicillin was supplied, if indicated, by Dr. Keefer and the Office of Scientific Research and Development. After establishment of the Civilian Penicillin Distribution Unit for distribution of penicillin in this country, its territories and possessions, the Foreign Economic Administration requested other countries to establish penicillin control committees to screen appeals and to distribute penicillin that could be made available from the United States for cases falling within the list of indications prepared by Dr. Keefer. The control committees cooperated fully and submitted monthly reports on their requirements, receipts, distribution, and stocks. Table 3 shows the amounts of penicillin exported.

Table 3.- Amounts of Penicillin Licensed
Monthly for Export by FEA

Unit: billion units

1944		1945	
June	1.0	January	15.5
July	2.0	February	18.6
August	2.7	March	27.5
September	3.0	April	35.0
October	4.0	May	90.0
November	6.3	June	135.0
December	10.0	July	200.0
		August	200.0
Total	29.0		
		Total	721.6

From the initiation of export of penicillin in June 1944 until April 1945 only producers of penicillin were permitted to export because of the limited supplies available and the controlled distribution procedure in the country of import. Following relaxation of limitations on civilian distribution in the United States in March 1945, penicillin control committees were no longer required in other countries, and anyone could export penicillin from the United States, provided that he had the penicillin or had a firm commitment from a supplier, and that the license application was received in time to permit it to be charged against Foreign Economic Administration monthly quotas established by the WPB Chemicals Bureau Requirements Committee on Drugs.

Recently, the export of 200 billion units per month has equalled the domestic consumption. This is an unusual situation in the drug field, where the export volume of a particular item rarely exceeds 25 percent of the domestic sales volume. The export demand for penicillin still is rising, and it is estimated that over 300 billion units will be the monthly demand for parenteral dosage forms of penicillin in other countries. The export market is eagerly awaiting the availability of oral, topical, and other dosage forms of penicillin. This is not likely to reduce the demand for parenteral penicillin, but, instead, will tend to increase the total export volume of penicillin and drug preparations containing it.

The United States shared penicillin with other countries for military and civilian use on the basis of an equitable division of the available supply and at comparable cost, thereby contributing to the improvement of public health throughout the world. Penicillin, thus, has helped to establish a better understanding among nations, which should aid in the establishment of world peace.

World Production

While the United States is the largest producer of penicillin, the penicillin achievements of several other countries are worthy of note. Production in the United Kingdom currently is averaging about 30 billion units per month. There are seven firms engaged in penicillin production with a combined potential of approximately 200 billion units per month scheduled to be attained by the end of the year. During the war, shortages of materials, equipment, and manpower necessarily delayed progress of the United Kingdom penicillin program.

In Australia, there is a government-owned penicillin plant which began operation in January 1944 and now produces approximately 10 billion units per month, with a potential of 20 billion units shortly to be obtained.

Canadian penicillin production started simultaneously with that of the United States. Three companies in Canada produce approximately 20 billion units per month, which is more than sufficient to meet all Canadian requirements.

Mexico is producing penicillin in relatively small amounts, but in no other country is commercial production of standardized penicillin appreciable. A number of nations are investigating the feasibility of erecting penicillin plants as an obvious early step in reconstruction and rehabilitation.

Fleming Fund

Penicillin, perhaps the outstanding life saving drug of all time, was a joint Anglo-American development. It was an example of cooperation between British and American scientists early in the war and before a basis for such community of effort was officially formalized. Our enemies developed no similar antibiotic and consequently suffered a higher mortality rate among their wounded. As an accolade to the discoverer of the drug, American penicillin producers presented to Sir Alexander Fleming, during his recent visit to the United States, a trust fund of $100,000 for financing research work to be conducted under his direction at St. Mary's Hospital Medical School, University of London. The University of Pennsylvania was named administrator of this fund in tribute to A. N. Richards, vice president of the university, who, as chairman of the Committee on Medical Research, Office of Scientific Research and Development, first supported and encouraged penicillin studies in this country. The results of Dr. Fleming's research activities will be available for use by anyone, without restriction.

Literature Cited

(1) Coghill, R. D., Chem. Eng. News, 22, 588 (1944).

(2) Jolliffe, C. B., Ibid., 23, 1450 (1945).

(3) Moyer, A. J., and Coghill, R. D. (in press).

(4) Murtaugh, J. J., and Levy, G. B., J. Am. Chem. Soc., 67, 1042 (1945).

(5) Ory, E. M., Meads, M., and Finland, M., J. Am. Med. Assoc., 129, 257 (1945).

(6) Schmidt, W. H., Ward, G. E., and Coghill, R. D., J. Bact., 49, 411 (1945).

(7) Welch, H., Putnam, L. E., Randall, W. A., and Herwick, R. P., J. Am. Med. Assoc., 126, 1024 (1944).